## REMARKS

### Amendments to the Claims

In the Office Action, Claims 2-7, 16-17, 19-20, 22-25, 33, 41, and 58-63 were withdrawn from consideration and Claims 1, 8-15, 18, 21, 26-32, 34-40, 42, 53-57, and 64-72 were rejected. In the amendment presented herewith, Claims 1, 37-40, and 65-72 have been amended and Claims 2-7, 22-25, 29-36, and 58-64 have been canceled, without prejudice. Claims 43-52 were previously canceled, without prejudice. Claims 1, 8-21, 26-28, 37-42, 53-57, 65-72 are pending; although, claims 16-17, 19-20, and 41 are still withdrawn from consideration.

Claim 1 has been amended by importing the structural limitations from Claim 36. As a result, Claim 36 has been canceled and the dependencies of Claims 37-40 have been updated. Further, the limitations of Claim 64 regarding tumor resection have been imported into Claim 1. As a result, Claim 64 has been canceled and the dependencies of claims 65-72 have been updated.

No new matter has been added by these amendments; therefore, examination is requested on the claims as amended herewith.

### Response to Rejection

In the Office Action, Claims 1, 8-15, 18, 21, 26-32, 34-40, 42, 53-57, and 64-72 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Izban *et al.* (Human Pathology 31(12):1482-1490, 2000) in view of Kahn *et al.* (US Patent 7,175,679). Specifically, the Examiner alleged that it would have been obvious to use a NF-κB inhibitor like BAY 11-7085 to treat colorectal cancer because NF-κB inhibitors are known to modulate COX, which is known to be involved in colorectal cancer. Applicants respectfully traverse this rejection, especially to the extent that it applies to the claims as amended herewith.

The Examiner's conclusion of obviousness is based on the following three premises:

A. BAY 11-7085 is a NF-κB inhibitor (vis-à-vis Izban *et al.*);

B. NF-κB modulates COX (vis-à-vis Kahn *et al.*); and

C. COX is involved in colon cancer (vis-à-vis Kahn *et al.*).

This line of reasoning is essentially that if A = B and B = C, then A = C is obvious. At first glance this may seem to be a logical conclusion; however, upon closer inspection it is fundamentally flawed. Specifically, while premise A is in fact true (BAY 11-7085 is a NF-κB

inhibitor), premise B is an over generalization and premise C is simply false. Thus, the Examiner's obviousness rejection is erroneous and should be withdrawn.

Beginning with premise B, this statement is true as articulated by the Examiner—COX expression is regulated by NF-κB. However, this statement is misused in the rejection. In particular, the Examiner over generalizes the fact that NF-κB regulates COX and incorrectly concludes that NF-κB inhibitors can be expected to have activity in diseases involving COX. This assumes too much. One cannot conclude that a particular NF-κB inhibitor will have any effect in diseases involving COX because, for instance, other pathways may be involved. Indeed, COX expression may not be involved at all in the disease state or its involvement may be irrelevant to NF-κB inhibition. A more accurate statement would have been that a given NF-κB inhibitor may or may not have activity in diseases involving COX; it depends on the particular disease and also on the particular inhibitor.

Even the Kahn *et al.* reference relied on by the Examiner falls short of supporting the broad application of premise B in the rejection. The Examiner uses Kahn *et al.* as evidence that any NF-κB inhibitor can be expected to have activity in COX mediated diseases like colorectal cancer; however, Kahn *et al.* does not fairly teach this. Kahn *et al.* only teaches that the particular oligopeptides disclosed therein inhibit NF-κB. It is not clear whether the oligopeptides of Kahn *et al.* actually affect COX; COX activity can only be assumed. But even if Kahn *et al.*'s oligopeptides are assumed to affect COX, it is not stated and cannot be inferred that such oligopeptides would have activity in diseases involving COX. Again, different pathways may be involved. So having said nothing about whether the particular oligopeptides actually have activity against COX mediated diseases, Kahn *et al.* certainly cannot be taken to suggest that compounds like BAY 11-7085 would have such activity.

In summary, the problem with premise B is that it takes the fact that NF-κB regulates COX expression and expands it to the over generalized conclusion that any NF-κB inhibitor can be expected to have efficacy against cancers mediated by COX. Anticancer activity of a NF-κB inhibitor may have nothing to do with COX expression. As additional evidence consider the following studies that show that BAY 11-7085 affects cancer cells through mechanisms besides COX:

1) Hu *et al.*, *Cancer Res* 2001, 61:6290-6, showed that BAY 11-7085 induced apoptosis of U937 leukemia cells in a p38-dependent fashion. They showed that BAY 11-7085 induced

the phosphorylation and activation of p38, and, that the p38 specific inhibitor (SB203580) reversed BAY 11-7085-induced apoptosis.

2) Cory *et al.*, *Anticancer Res* 2008, 28(2A):681-6, showed that BAY 11-7085-induced apoptosis of L1210 cells could be reversed by N-acetylcysteine. The effect of N-acetylcysteine was related to changes in the levels of Grp78 and Gadd153, proteins involved in the endoplasmic reticulum stress pathway. These effects were specific to BAY 11-7085 since the ability of MG-132, flavopiridol, gemcitabine and PRIMA-1 to induce apoptosis of L1210 cells was not diminished by N-acetylcysteine.

3) Vega *et al.*, *J Immunol* 2005, 175:2174-83, showed that rituximab and BAY 11-7085 induced apoptosis of Ramos non-Hodgkin's lymphoma cells through inhibition of NF-kB and indirectly, Bcl-xL expression. Bcl-xL expression is known to be regulated by NF-kB. Overexpression of Bcl-xL in the cells rendered them resistant to apoptosis induced by rituximab and BAY 11-7085 further implicating Bcl-xL in the apoptotic mechanism of these drugs.

4) Huerta-Yepez *et al.*, *Oncogene* 2004, 23:4993-5003, showed that multiple prostate cancer cell lines that are resistant to TRAIL-induced apoptosis became TRAIL-sensitive by pretreatment with NO-donor drugs. BAY 11-7085 also sensitized the same cells to TRAIL-induced apoptosis. It was shown that Bcl-xL expression was inhibited by NO-donor drugs or BAY 11-7085. Furthermore, inhibition of Bcl-xL with 2-methoxyantimycin A(3) sensitized the cell lines to TRAIL further implicating Bcl-xL as the downstream target of NO-donor drugs and BAY 11-7085.

5) Mabuchi *et al.*, *J Biol Chem* 2004, 279:23477-85, showed that BAY 11-7085 increased cisplatin-induced apoptosis of A2780 and Caov-3 ovarian cancer cells. It was shown that BAY 11-7085 increased the efficacy of cisplatin-induced apoptosis by decreasing XIAP expression. XIAP is a cell survival gene whose expression is regulated by NF-κB.

Turning now to premise C, the Examiner finds that COX's are involved in colorectal cancers. While this may be true, there is no evidence that COX inhibitors are effective in treating colon cancers. One study (El-Rayes *et al.*, *Cancer Chemother Pharmacol* 2008, 61:283-9) showed that the addition of the COX-2 inhibitor celecoxib failed to improve the efficacy of irinotecan and capecitabine in patients with advanced colorectal cancer. Another study (Becerra *et al.*, *Int J Cancer* 2003, 105:868-72) showed that another COX-2 inhibitor (rofecoxib) failed to

improve the efficacy of 5-FU and leucovorin in patients with advanced colorectal cancer. These studies make clear that just because COX may be involved, COX inhibitors do not show clinical efficacy in advanced colorectal cancer treatment.

It is clear that even though BAY 11-7085 is a NF-κB inhibitor, and COX expression is regulated by NF-κB, one cannot conclude (as the Examiner does) that a particular NF-κB would have a meaningful effect on COX. It is an even further stretch to conclude that even if a compound had COX activity, that that activity would result in therapeutic properties. Therefore, the Rejection of the claims over the cited references should be withdrawn.

Notwithstanding the above, the claims have been amended to recite inhibiting "anchorage dependent cancer" in a subject that "has had a tumor resected." The cited references say and suggest nothing about this indication. Therefore, Applicants again respectfully request that the present rejection be withdrawn.

## CONCLUSION

In light of the amendments and arguments presented herein all of the rejections are believed to be overcome. As such, Applicants respectfully request notification of same. The Examiner is encouraged to contact the undersigned if it may advance prosecution.

Enclosed herewith is payment in the amount of $735.00, which includes the $555.00 fee under 37.C.F.R. §1.17(a)(3) for the Three-Month Extension of Time and the $180.00 fee required under 37 C.F.R. § 1.97(c)(2) for the Information Disclosure Statement. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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/Christopher L. Curfman/ November 14, 2008

Christopher L. Curfman Date